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DATA EVALUATION RECORD

TRICHLORFON

TERATOLOGY IN RATS

CITATION: Gofmekler VA, Tabakova SA. 1970. The effect of trichlorfon on embryogenesis in rats. Pharmacology and Toxicology (Moscow) 33(6):735-737.

REVIEWED BY:

Curt Lunchick, M.S.
Project Scientist
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: Curt Lunchick

Date: 25 July 83

John R. Strange, Ph.D.
Department Director
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: John R. Strange

Date: 25 July 1983

APPROVED BY:

Irving Mauer, Ph.D.
EPA Scientist

Signature: Irving Mauer

Date: 07-25-83

DATA EVALUATION RECORD

STUDY TYPE: Inhalation teratology in rats.

CITATION: Gofmekler VA, Tabakova SA. 1970. The effect of trichlorfon on embryogenesis in rats. Pharmacology and Toxicology (Moscow) 33(6):735-737.

ACCESSION NUMBER: Not available.

MRID NUMBER: Not available.

LABORATORY: Sysin Institute of Public and Communal Hygiene, Moscow, USSR.

TEST MATERIAL: Trichlorfon, purity and source not stated.

PROTOCOL:

1. Trichlorfon was studied for its teratogenic potential. Further identification of the test substance and its purity were not specified.

2. Ninety-nine pregnant female white rats, weighing 170 - 220 g were used in the test system. The strain of rat was not specified. The female rats were assigned to treatment groups after mating; however, the method of assignment and the number of animals per group were not given.

3. The pregnant test animals were divided into five test groups, one of which was a control group. No information was provided by the author indicating that the animals were equally distributed among treatment groups. After mating, animals in the four treatment groups were "inoculated continuously for a period of 20 days with trichlorfon vapors." The reviewer assumes that "inoculated continuously" implies 24 hours per day. The trichlorfon concentraton levels utilized on the study were 0.005 0.02, 0.2, and 9 mg/m^3. Trichlorfon content was determined by the "nephelometric method." The mean trichlorfon concentrations and the upper and lower concentrations of trichlorfon at each dose level during the exposure were not reported. No description of the chamber, exposure method (full body or head only), vapor generation methodology, or other pertinent data regarding the exposure methodology were described.

4. The animals were sacrificed by cervical dislocation after 20 days of exposure and the contents of the uterus examined. The females were examined for evidence of pre- and post-implantation losses. The

fetuses were examined for external and internal developmental abnormalities. Visceral examinations were conducted using the technique of Wilson on fetuses that were preserved in Buen (sic. Bouin's) fluid for seven days. Skeletal examinations were performed on fetuses stained with alizarin. The report does not specify if all the fetuses examined were viable; nor is the percentage of fetuses per litter assigned to visceral or skeleton examinations specified. The methodology for staining the fetuses for skeletal examination was not detailed. "Changes in certain biochemical indexes of the female and embryo organs, as well as the placenta, and the presence of histopathological and histochemical shifts" were examined. It is not clear from the report if the fetuses used for the biochemical indices were also used for visceral or skeletal examinations.

5. "The calculation of statistical reliability was performed by the peak-to-peak method" (described by R.N. Biryukova, Gigiyena i Sanitariya, No. 7, 1962, page 43). The parameters tested were examined at significance levels of 95 percent, 99 percent, and 99.9 percent.

RESULTS:

No data on maternal or fetal observations, body weights, and maternal food consumption were reported. It was reported that "When studying female fertility and embryo deaths both before and after implantation, no reliable deviations from the norm were seen."

The following skeletal changes were reported in fetuses from the 0.005 and 0.02 mg/m^3 dose groups: "incomplete ossification of the small ossicles in the front and back paws, spinal curvature, and a marked cartilaginous pattern in the ribs due to impregnation of the cartilage sections by blood components." One fetus [it was not specified if the fetus was from the 0.005 or 0.02 mg/m^3 dose level] was observed to have "impairment of the proper shape of the mouth opening" [Cleft palate?].

The following skeletal and visceral changes were reported in fetuses from the 0.2 and 9 mg/m^3 dose groups: "the changes described above" for the 0.005 and 0.02 mg/m^3 groups, "incomplete ossification of the spine and rib ends is observed, as well as the appearance of 'superfluous' ossicles in sections of the lower extremities." "Underdevelopment of the brain, externally manifested by cerebral enlargement [hydrocephaly?], hemorrhaging in the peritoneal cavity and individual organs, and enlargement of the carotid artery [not graded]." were the visceral abnormalities reported. Externally, "some embryos reach unusually large sizes and appear to be incoherent. A great deal of fluid is detected in the cavity incisions" was observed. The "percentage of skeletal disorders increased and take on a greater variability" at the two highest dose levels. The number of fetuses with each malformation, the number of litters with malformed fetuses, specifity regarding the malformations observed in each treatment group, and any data pertaining to the control group were not reported.

"The determination of shifts was also performed by means of certain biochemical indexes: a decrease in the content of ascorbic acid in the placenta, brain, and liver of both females and embryos alike, as well as an increase in the overall and individual content of nucleic acids in the organs of both females and embryos alike. These changes suggest a toxic effect by trichlorfon on the organism of the female, and consequently, on the embyro itself (an ascorbic acid biosynthesis effect and the disruption of protein systhesis)."

"In the placenta of animals subjected to Trichlorfon exposures in concentrations of 9 and 0.2 mg/m^3, histopathological and histochemical changes are detected: contraction in the labyrinthine region of the fetal placenta, apparently due to an inhibitive effect on the conversion of cellular trophoblast into plasmodial, excessive nuclear polymorphism within the trophoblast cells, the degeneration and hyperchromatosis of certain cells in the syncytial trophoblast, a change in the endothelium of the embryonic capillaries, and a decrease in the content of ascorbic acid and glycogen in the placenta. The combinations of these changes makes it possible to verify a decrease in the functional activity of the placenta. Concurrent with this, reactions are observed which suggest compensatory processes: enlargement in the individual gaps of the labyrinth, an increased content of hemoglobin, and an increase in the amount of binuclear cells."

CONCLUSIONS:

Pregnant rats were exposed to trichlorfon vapors at the following concentrations continously for 20 days: 0.005, 0.02, 0.2, and 9 mg/m^3. At the end of the exposure the animals were sacrificed and the uterine contents examined. The data, as reported, prevent the reviewer from drawing definitive conclusions regarding the teratogenicity of trichlorfon. The description in the report of the malformations indicate that an increase in skeletal and visceral abnormalities occurred with increasing concentrations of trichlorfon. Without the inclusion of any data regarding possible maternal toxicity, it is impossible to determine if the fetal malformations observed were resultant from a frank teratogenic action by trichlorfon or were from possible maternal stress due to maternal toxicity from continuous exposure over 20 days to trichlorfon of concentrations as great as 9 mg/m^3.

CORE CLASSIFICATION: Supplementary data.

The following major deficiencies were noted:

- Fetal teratogenic evaluation observations were not reported as number of litters with malformed fetuses per group, number of fetuses with each malformation per group, or number of malformed fetuses per group.
- No fetal teratogenic data was provided for the control group.
- The terminology used to describe the fetal malformations was poor and vague.
- No clinical observations or maternal body weight data were given.
- The number of animals per dose group was not given.
- The strain of rats was not given.
- The source and purity of the trichlorfon were not given.